

Brief Summary of the Molecular and Clinical Genetics Panel Meeting – March 27, 2014

Introduction:

The Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on March 27, 2014 to make recommendations and vote on the premarket approval application for the *Cologuard* device sponsored by Exact Sciences. *Cologuard* is intended for use as an adjunctive screening test for the detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer or pre-malignant colorectal neoplasia. *Cologuard* is not intended as a replacement for diagnostic colonoscopy. A positive result in *Cologuard*, as with any screening test, should be followed by colonoscopy. *Cologuard* is intended for patients who are typical candidates for colorectal cancer screening: adults of either sex, 50 years or older, who are at average risk for colorectal cancer.

Panel Deliberations/FDA Questions:

Panel Question 1: Effectiveness and Risk vs. Benefit

- a. Do these conclusions adequately demonstrate effectiveness of *Cologuard* within the contexts of the proposed intended use and current recommendations for CRC screening?

Yes.

The Panel recommended that the test be described as an “alternative” instead as an adjunctive screening test in the intended use. The Panel also recommended adding “surveillance” to “diagnostic colonoscopy.”

- a. Based on the results of the pivotal clinical study, do the data provided allow for adequate assessment of the benefits and risks of *Cologuard*?

Yes.

Panel Question 2: Additional Labelling for subgroups

Are there patient subgroups, such as age (e.g., ages 75-79, 80-84, 85 and above), gender, and race/ethnicity where considerations for device performance merit additional labeling?

Yes.

The Panel recommended that labeling should indicate that the false positive rate increases with increasing age. There should not be an upper age limit restriction in the labeling. A warning in the labeling against the use of the device in certain races and ethnicities should not be included because there are insufficient data to support such a warning. These differences found in the clinical study,

however, could be included in the labeling to better inform health care providers. Differences between males and females in device performance should not be emphasized in the labeling because the sensitivity rate in both groups is high, and therefore such a label would not be clinically useful.

Panel Question 3: Follow-up

What is appropriate labeling to assure safety and effectiveness for follow-up evaluation of patients testing negative with *Cologuard*? The FDA would like feedback on follow-up test interval and modality, use of guidelines, and other possible follow-up approaches.

The Panel recommended including language about how patients testing negative with *Cologuard* should be followed up with the standard of care for colorectal cancer screening.

Panel Question 4: One- time screening and additional screening concerns

- a. *Cologuard* claims do not specify a testing interval. Please discuss whether a longitudinal study should be required to address long-term safety and effectiveness

Yes.

The Panel stated that a longitudinal study should be required to determine the programmatic performance and value of repeat testing. The study as designed may yield results that are difficult to interpret. The Panel recommended a two-arm randomized trial with one arm including *Cologuard* at baseline and year three, and the other arm including *Cologuard* yearly for three years. All patients remaining in the study at the end of three years will have a colonoscopy. FIT testing would not be necessary in this longitudinal study design. The Panel believed that FDA should not extrapolate and specify a testing interval in the labeling at this point in time because additional long-term data are required. The Panel recommended against using the words “one-time testing” in the intended use statement because they felt this wording is too restrictive. The labeling should be updated after the evaluation of longitudinal data.

Panel Question 5: Post Approval Study

- a. Is comparison to a recommended CRC screening option (e.g., annual FIT) needed to evaluate study results and to mitigate study limitations as currently proposed by the sponsor (such as controlling for incident CRC cases, lack of objective criteria for evaluating study results)?
- b. Is the sponsor’s proposed post-approval study adequate to address the following issues?
 - i. Performance (e.g., number of test negative to positive conversions, diagnostic yield of significant findings, predictive values, adherence to screening and diagnostic follow-up);
 - ii. Performance across different clinicopathologic characteristics;

- iii. Safety concerns (e.g., in the sponsor's proposal, subjects would forgo annual FIT screening during the study duration and repeat *Cologuard* testing will occur after 3 years).
- c. Are there any additional considerations that should be taken into account for the post-approval study?

The Panel recommended that the proposed post approval study should be changed to the one described in question 4. The study should not prespecify different performance criteria for advanced adenoma versus colorectal cancer, but these data should be analyzed. For example, the study should be designed with colorectal cancer as the primary endpoint, but to include plans to analyze advanced adenomas. Different demographics such as ethnic groups should also be evaluated, but this should not be the focus of the study.

Vote:

The panel voted on the safety, effectiveness, and risk benefit ratio of Exact Sciences *Cologuard*.

On Question 1, the panel voted 10 -0 that the data shows that there is reasonable assurance that *Cologuard* is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 10 -0 that there is reasonable assurance that *Cologuard* is effective for patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 10 -0 that the benefits of *Cologuard* do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

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